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Noninvasive Risk Assessment Early After a Myocardial Infarction

The REFINE Study

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Objectives This study sought to determine whether combined assessment of autonomic tone plus cardiac electrical substrate identifies most patients at risk of serious events after myocardial infarction (MI) and to compare assessment at 2 to 4 weeks versus 10 to 14 weeks after MI.

Background Methods to identify most patients at risk of serious events after MI are required.

Methods Patients (n = 322) with an ejection fraction (EF) <0.50 in the initial week after MI were followed up for a median of 47 months. Serial assessment of autonomic tone, including heart rate turbulence (HRT), electrical substrate, including T-wave alternans (TWA), and EF was performed, interpreted blinded, and categorized using prespecified cut-points where available. The primary outcome was cardiac death or resuscitated cardiac arrest. All-cause mortality and fatal or nonfatal cardiac arrest were secondary outcomes.

Results Mean EF significantly increased over the initial 8 weeks after MI. Testing 2 to 4 weeks after MI did not reliably identify patients at risk, whereas testing at 10 to 14 weeks did. The 20% of patients with impaired HRT, abnormal exercise TWA, and an EF <0.50 beyond 8 weeks post-MI had a 5.2 (95% confidence interval [CI] 2.4 to 11.3, p < 0.001) higher adjusted risk of the primary outcome. This combination identified 52% of those at risk, with good positive (23%; 95% CI 17% to 26%) and negative (95%; 95% CI 93% to 97%) accuracy. Similar results were observed for the secondary outcomes.

Conclusions Impaired HRT, abnormal TWA, and an EF <0.50 beyond 8 weeks after MI reliably identify patients at risk of serious events. (Assessment of Noninvasive Methods to Identify Patients at Risk of Serious Arrhythmias After a Heart Attack; http://www.clinicaltrials.gov/ct/show/NCT00399503?order=1; NCT00399503) (J Am Coll Cardiol 2007;50:2275–84) © 2007 by the American College of Cardiology Foundation

Patients who survive a myocardial infarction (MI), particularly those with residual left ventricular (LV) dysfunction, are at risk of serious events (1,2). Although the implantable cardioverter-defibrillator (ICD) reduces mortality late after MI (3,4), it has not been shown to improve survival early after MI (5–7). The explanations for the lack of benefit with ICD therapy are complex, but may relate to LV remodeling or other time-dependent effects (8). The lack of benefit may also be related to a higher risk of nonsudden versus sudden death in the initial 12 to 18 months after MI (1).

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Reliable identification of most MI survivors at risk of serious events has remained elusive. Noninvasive measures of autonomic tone (9,10) and cardiac electrical substrate (11–13) have been developed to identify patients at risk of

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Abbreviations and Acronyms

AUC = area under the receiver-operator characteristic curve
BRS = baroreflex sensitivity
CI = confidence interval
ECG = electrocardiograph/electrocardiographic
HRT = heart rate turbulence
HRV = heart rate variability
ICD = implantable cardioverter-defibrillator
LV = left ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
TWA = T-wave alternans
VPB = ventricular premature beats

death and serious arrhythmias after MI. Although marked abnormalities in autonomic tone alone identify patients at risk, this approach is limited by low sensitivity (9,10,14). Combining multiple measures of autonomic tone (15,16) or combining multiple measures of electrical substrate (17) has not been shown to improve diagnostic accuracy. Combining measures of autonomic tone with measures of electrical substrate may enhance risk assessment (15,18), but this strategy remains unproven in the era of contemporary post-MI management (19).

The REFINE (Risk Estimation Following Infarction, Noninvasive Evaluation) cohort study was designed to evaluate the utility of combined assessment of autonomic tone plus cardiac electrical substrate to identify the majority of patients at risk for cardiac death or resuscitated cardiac arrest after MI and to determine the optimal time to assess risk early after MI.

Methods

Recruitment. Participants were enrolled from 6 Canadian hospitals, representing 4 community-based and 2 tertiary referral institutions. The ethics review board at each institution approved the protocol. All patients provided written, informed consent. Patients were enrolled from May 2001 through July 2004. Follow-up was completed in December 2006.

Patients were considered eligible if they had a confirmed MI (20) and a left ventricular ejection fraction (LVEF) <0.40 in the initial 48 h of the index MI or an LVEF <0.50 measured beyond the initial 48 h. Inclusion was limited to those with at least mild LV dysfunction because patients with preserved LV function after MI are at extremely low risk of serious events (9). Patients with permanent atrial fibrillation, a ventricular paced rhythm, a previously implanted ICD, or a clinical indication for an ICD at the time of enrollment (21) were ineligible. Participant flow is detailed in Figure 1. Most individuals excluded were deemed ineligible because of an LVEF >0.50 in the initial week after MI. Outcome data on excluded patients were not prospectively collected.

Testing details. All 322 patients underwent assessment of parameters at 2 to 4 weeks (acute) and at 10 to 14 weeks (nonacute) after MI. Test results were not disclosed to participants or their treating physicians. Participants underwent a submaximal exercise test to assess repolarization

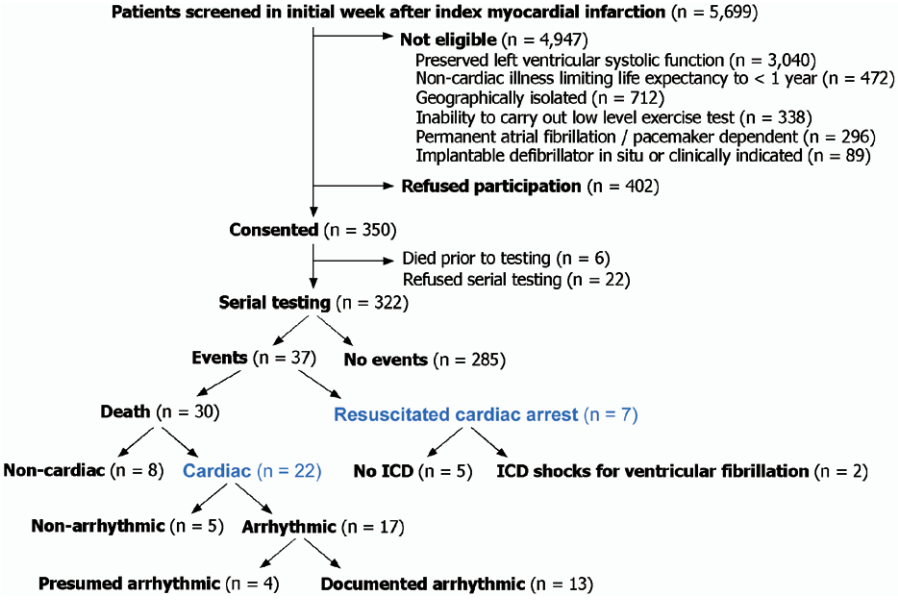

Figure 1 Patient Selection and Outcomes

A total of 322 patients with residual left ventricular dysfunction in the initial week after a myocardial infarction completed serial testing. They were enrolled from a larger population, most of whom were deemed ineligible due to preserved left ventricular function, a serious comorbid illness, or an inability or unwillingness to undergo serial testing. During 47 months of follow-up, 30 deaths were observed. Of these, 22 were categorized as cardiac and 17 as cardiac arrhythmic. Additionally, 7 resuscitated cardiac arrests occurred, only 2 of which were in patients with an implantable cardioverter-defibrillator (ICD) at the time of the event. Events comprising the primary outcome are shown in **blue**.

alternans (TWA) (17,22), followed by a 20- to 30-min high-resolution digital electrocardiographic (ECG) recording, from which signal-averaged QRS width (18) and Holter TWA were measured (13). Participants then underwent phenylephrine-induced baroreflex sensitivity (BRS) testing (9). An 18- to 24-h digital ambulatory ECG recording was then performed to assess heart rate variability (HRV) (23) and heart rate turbulence (HRT) (10). The scheduled dose of beta-blocker immediately before testing was delayed to facilitate achievement of the desired heart rate on the exercise test. The LVEF was assessed in the initial week after MI using echocardiography (156 patients), contrast ventriculography (140 patients), or radionuclide ventriculography (26 patients). All 322 patients underwent assessment of LVEF via radionuclide ventriculography at 8 weeks to 10 weeks after MI.

Dichotomy limits. The dichotomy limits used to define impairment were chosen to optimize sensitivity because traditional dichotomy limits do not optimally predict events when combined (24). The pre-specified values for defining abnormal HRV were standard deviation of intervals values <105 versus ≥ 105 ms (23). Impaired BRS was defined by an average slope of ≤ 6.1 versus >6.1 ms/mm Hg (9). Altered HRT was defined by abnormalities in either HRT onset or slope versus both parameters being normal (10). The 14 (4%) patients without ventricular premature beats (VPB) at the 2- to 4-week (acute) and the 22 (7%) patients without VPB at the 10- to 14-week (nonacute) early post-MI test visits were categorized as having normal HRT (25). The pre-specified definitions for abnormal electrical substrate were an increased signal-averaged QRS duration of ≥ 114 versus <114 ms (18), and a non-negative versus negative exercise TWA result (26,27). Given the lack of prior data for the Holter TWA method, receiver-operator characteristic curves were generated using the continuous data over a 32-beat window as the raw signal minus the noise and as the raw where the signal to noise ratio was ≥ 1.2. A cutoff of ≥ 5 versus <5 μV for the Holter TWA method using either method provided similar sensitivity and specificity to that achieved with exercise TWA in predicting the secondary outcome of fatal or nonfatal cardiac arrest at the nonacute test visit. A cut point of <0.50 was used to define an abnormal LVEF value on the week 8 assessment.

Events. An independent committee, unaware of the test results, reviewed all events. Deaths were categorized as cardiac or noncardiac. Cardiac deaths were then categorized as arrhythmic or nonarrhythmic (28). The pre-specified primary outcome was cardiac death or resuscitated cardiac arrest (9,19). All-cause mortality (29) and fatal or nonfatal cardiac arrest were pre-specified secondary outcomes.

Sample size estimate. The study was designed to have 85% power to detect at least a 3-fold higher risk of the primary outcome in patients with abnormalities in both autonomic tone and electrical substrate versus the remaining population, assuming that up to 25% of the population would have abnormalities in both autonomic tone and electrical substrate (18).

Statistical analyses. The capacity of the noninvasive tests to independently predict the primary and secondary outcomes was assessed using Cox multivariate models from which hazard ratios and 95% confidence intervals (CIs) were obtained (30). Outcome status was obtained on all 322 patients. The proportional hazards assumption was confirmed to be valid for each test variable using log-log plots and assessment of weighted residuals (31). Given the potential impact of age, gender, history of prior MI, and LVEF, these variables were pre-specified to be included in the multivariate models. History of diabetes also was found to be a significant predictor of outcome and was included in the models. Noninvasive test results that were not analyzable due to technical reasons were imputed as normal. This included 14 (4%) acute and 11 (3%) nonacute Holter recordings, 17 (5%) acute and 16 (5%) nonacute high-resolution ECG recordings, 7 (2%) acute and 11 (3%) nonacute exercise TWA tests, and 15 (5%) acute and 11 (3%) nonacute BRS assessments. Univariate logistic regression models were used to calculate the areas under the receiver-operator characteristic curve (AUC) for predicting the primary and secondary outcomes using the aforementioned dichotomy limits for the noninvasive tests. The time to development of the primary and secondary outcomes was graphically displayed by constructing Kaplan-Meier time-to-event curves, and differences in survival were assessed using the log-rank test statistic. Correlation between TWA methods was assessed using the Kappa statistic (32). All analyses were performed using Stata 9.2MP (Stata Corp., College Station, Texas). Two-sided p values ≤ 0.05 were considered statistically significant.

Results

Follow-up and clinical events. The median duration of follow-up was 47 months (interquartile range 37 to 56 months), and during this time 16 patients (5%) received an ICD because of a resuscitated cardiac arrest (5 patients) or persistent severe LV dysfunction. Thirty adjudicated deaths and 7 adjudicated resuscitated cardiac arrests occurred during follow-up for the 322 patients who completed serial testing (Fig. 1). Two resuscitated cardiac arrests occurred in patients with an ICD placed before that event. One patient died after the initial event, but before the follow-up noninvasive test visit. This death was categorized as cardiac, nonarrhythmic.

Characteristics. The characteristics of the 322 patients who underwent serial testing, overall, and by whether they did versus did not suffer the primary outcome, are shown in Table 1. Most were male, and approximately one-quarter had a history of a prior MI. The median time from the prior MI to the index MI was 7 years. Patients who did versus those who did not suffer the primary outcome in follow-up were similar in most respects. However, a history of diabetes

Table 1 Patient Characteristics Overall, and Stratified by the Development of the Primary Outcome

	All Patients (n = 322)	Cardiac Death or Cardiac Arrest (n = 29)	Remaining Patients (n = 293)
Median age, yrs (IQR)	62 (53–70)	64 (54–71)	62 (53–70)
Male, %	85	83	85
History of prior MI, %	23	34	22
History of diabetes, %	22	38*	21
History of hypertension, %	45	55	44
Median creatinine, μmol/l (IQR)	84 (73–97)	85 (76–100)	84 (72–98)
Index MI			
Median troponin I (IQR)	4.0 (1.2–12.9)	3.7 (1.0–8.3)	4.1 (1.2–13.2)
Q-wave MI, %	68	59	69
Anterior location, %	62	56	63
Early revascularization, ≤24 h			
Direct angioplasty, %	45	37	47
Glycoprotein IIb/IIIa inhibitor, %	34	31	34
Thrombolytic therapy, %	21	21	21
Later revascularization, >24 h			
Delayed angioplasty, %	21	21	21
Coronary artery bypass, %	14	10	13
Median LV ejection fraction			
Within 7 days of index MI (IQR)	0.40 (0.35–0.44)	0.38 (0.27–0.40)†	0.40 (0.35–0.45)
Week 8 after index MI (IQR)	0.47 (0.38–0.55)	0.40 (0.30–0.41)†	0.49 (0.39–0.49)

*p = 0.05; †p < 0.01 for comparison of patients who did versus those who did not reach primary outcome.
IQR = interquartile range; LV = left ventricular; MI = myocardial infarction.

was more common in the group who developed the primary outcome.

Medication usage, revascularization, and ejection fraction. Participants reported a high rate of appropriate medical therapy use at the time of enrollment and throughout follow-up (Table 2). Medication usage was similar in patients who did versus did not develop the primary outcome in follow-up (exact p values ≥0.3). Most patients (81%) underwent direct angioplasty at the time of the index MI or revascularization soon after the index MI (Table 1). A 19% relative (8% absolute) increase in mean LVEF was observed over the initial 8 weeks after MI overall (*t* test $p < 0.001$). Patients who developed the primary outcome in follow-up had significantly smaller increases in LVEF than did the remaining patients (*t* test $p < 0.01$).

Noninvasive assessment 2 to 4 weeks after MI. No single measure of autonomic tone and no single measure of electrical substrate predicted a significantly higher independent risk of the primary outcome in the acute testing period (Table 3, left). Similar results were observed when the patient who died between test visits was included. The presence versus absence of frequent VPB, defined as ≥10 VPB/h, was not associated with a higher independent risk of the primary outcome. Each parameter was limited by suboptimal predictive utility, as evidenced by modest dichotomized AUC values (Table 4, left). Similar results were observed for the secondary outcomes.

Noninvasive assessment 10 to 14 weeks after MI. Impaired BRS, impaired HRT, and abnormal TWA each predicted a significantly higher independent risk of the primary outcome when measured at 10 to 14 weeks after MI (Table 3, right). Each individual parameter had higher predictive utility in the nonacute versus acute post-MI period, as evidenced by the larger dichotomized AUC values (Table 4, right). Impaired HRV and signal-averaged QRS width did not independently predict the primary outcome. Similar results were observed for the secondary outcomes. The presence versus absence of frequent VPB was associated

Table 2 Patient-Reported Medication Use at Time of Enrollment and During Follow-Up

		Months After Myocardial Infarction					
	Enrollment	1	3	6	12	24	36
Number of patients with data available	322	322	316	312	304	280	188
Antiplatelet agent (%)	99	99	96	94	93	92	94
Beta-blocker (%)	92	91	91	89	91	89	89
Statin (%)	89	87	87	86	87	86	86
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (%)	94	90	90	88	84	86	86

Table 3 Adjusted Hazard Ratios for the Capacity of the Individual Parameters to Predict Development of the Primary Outcome (Cardiac Death or Resuscitated Cardiac Arrest) in the Acute and Nonacute Early Post-MI Periods

Impairment	Hazard Ratio* (95% Confidence Interval) p Value	
	2 to 4 Weeks After Index MI	10 to 14 Weeks After Index MI
Autonomic tone		
Heart rate variability (SDNN <105 vs. ≥105 ms)	1.24 (0.50–3.27)	2.15 (0.95–4.87)
	0.65	0.066
Baroreflex sensitivity (<6.1 vs. ≥6.1 ms/mm Hg)	2.01 (0.76–5.27)	2.71 (1.10–6.67)
	0.16	0.030
Heart rate turbulence (abnormal onset or slope vs. both normal)	1.42 (0.54–3.75)	2.91 (1.13–7.48)
	0.47	0.026
Electrical substrate		
Exercise repolarization alternans (non-negative vs. negative)	2.42 (0.96–7.71)	2.75 (1.08–7.02)
	0.060	0.034
Holter repolarization alternans (≥5 vs. <5 μV)	2.09 (0.95–4.60)	2.94 (1.10–7.87)
	0.067	0.031
QRS width (≥114 vs. <114 ms)	1.35 (0.54–3.36)	1.75 (0.76–3.99)
	0.53	0.19
History of diabetes	2.68 (1.21–5.92)	2.72 (1.23–5.99)
	0.014	0.013
Left ventricular ejection fraction (≤0.30 vs. >0.30)	3.06 (1.39–6.74)	3.30 (1.43–7.63)
	0.005	0.005

*Cox model hazard ratio adjusted for age, gender, history of previous MI, history of diabetes, and ejection fraction.
MI = myocardial infarction; SDNN = standard deviation of intervals.

with a trend toward a higher independent risk of the primary outcome (hazard ratio 2.2, 95% CI 0.9 to 5.3, p = 0.07).

TWA assessment. The TWA methods predicted similarly higher independent risks of the primary outcome (Table 3). Overall, the agreement between exercise and Holter TWA methods was modest (kappa = 0.17, p = 0.002), but high agreement was observed between the techniques among patients who developed the primary outcome (kappa = 0.49, p = 0.009) and those who died (kappa = 0.41. p = 0.02) or suffered a cardiac arrest (kappa = 0.48, p = 0.02).

Table 4 AUC for the Individual Parameters in Predicting the Primary Outcome (Cardiac Death or Resuscitated Cardiac Arrest) in the Acute and Nonacute Early Post-MI Periods

Impairment	AUC*	
	2 to 4 Weeks After Index MI	10 to 14 Weeks After Index MI
Autonomic tone		
Heart rate variability (SDNN <105 vs. ≥105 ms)	0.59	0.62
Baroreflex sensitivity (<6.1 vs. ≥6.1 ms/mm Hg)	0.60	0.66
Heart rate turbulence (abnormal onset or slope vs. both normal)	0.58	0.66
Electrical substrate		
Exercise repolarization alternans (non-negative vs. negative)	0.61	0.62
Holter repolarization alternans (≥5 vs. <5 μV)	0.60	0.62
QRS width (≥114 vs. <114 ms)	0.55	0.56
History of diabetes	—	—
Left ventricular ejection fraction (≤0.30 vs. >0.30)	0.62	0.62

*Unadjusted logistic regression model for the pre-specified dichotomy limits shown.
AUC = area under the receiver-operator characteristic curve; other abbreviations as in Table 3.

Combined parameter assessment. No combination of impaired autonomic tone plus abnormal electrical substrate measured at 2 to 4 weeks after MI independently predicted the development of the primary outcome or the secondary outcomes. When assessed at 10 to 14 weeks after MI, both impaired BRS plus abnormal TWA and impaired HRT plus abnormal TWA each predicted a significantly higher independent risk of the primary outcome (Table 5, left). The dichotomized AUC values were higher for the combinations that included HRT with either TWA method because of enhanced sensitivity (Table 6). Patients with impaired HRT plus abnormal Holter TWA at 10 to 14 weeks after MI were at higher risk for the primary and secondary outcomes overall and within multiple subgroups, including stratification by LVEF of ≤0.30 versus >0.30 beyond 8 weeks after MI (Fig. 2). Similar results were observed for the other combinations of parameters. Adjustment for frequent VPB did not alter these relationships. The combination of HRT and exercise TWA at 10 to 14 weeks after MI identified 17 of the 29 (59%) primary outcome events. Of the 12 events not predicted by this combination, 9 were cardiac deaths (4 arrhythmic and 5 nonarrhythmic) and 3 were resuscitated cardiac arrests.

Table 5 Adjusted Hazard Ratios for the Capacity of the Noninvasive Parameters Alone and Combined With Ejection Fraction to Predict the Development of the Primary Outcome (Cardiac Death or Resuscitated Cardiac Arrest)

Noninvasive Parameters Alone		Noninvasive Parameters Plus LVEF	
Parameters Alone (10 to 14 Weeks Post-MI)	Hazard Ratio* (95% CI) p Value	Parameters Plus LVEF (Beyond 8 Weeks Post-MI)	Hazard Ratio† (95% CI) p Value
Abnormal exercise TWA + BRS	3.27 (1.42–7.00)	Abnormal exercise TWA + BRS + LVEF <0.50	5.22 (2.25–12.13)
(n = 52) vs. others	0.005	(n = 31) vs. others	<0.001
Abnormal Holter TWA + BRS	3.17 (1.42–6.94)	Abnormal Holter TWA + BRS + LVEF <0.50	4.77 (2.08–10.90)
(n = 53) vs. others	0.005	(n = 32) vs. others	<0.001
Abnormal exercise TWA + HRT	3.58 (1.52–7.38)	Abnormal exercise TWA + HRT + LVEF <0.50	5.08 (2.17–11.89)
(n = 91) vs. others	0.003	(n = 64) vs. others	<0.001
Abnormal Holter TWA + HRT	4.18 (2.06–8.32)	Abnormal Holter TWA + HRT + LVEF <0.50	6.22 (2.88–13.42)
(n = 93) vs. others	0.001	(n = 55) vs. others	<0.001

*Cox model hazard ratio adjusted for age, gender, history of previous MI, history of diabetes, and ejection fraction. †Cox model hazard ratio adjusted for age, gender, history of previous MI, and history of diabetes.

BRS = baroreflex sensitivity; CI = confidence interval; HRT = heart rate turbulence; LVEF = left ventricular ejection fraction; MI = myocardial infarction; TWA = T-wave alternans.

LVEF. Although all patients had LVEF values ≤0.50 at study entry, only 180 patients (56%) had LVEF values of <0.50, at 8 weeks after MI. An LVEF ≤0.30 measured at both the initial week and at 8 weeks after MI were each predictive of a higher risk of the primary outcome, but the AUC values for these dichotomy limits were modest (Table 4). Logistic regression models were used to assess whether the noninvasive tests provided distinct information on prognosis, separate from LVEF (33). Development of the primary outcome was used as the dependent variable. The LVEF, Holter TWA voltage, HRT onset, and HRT slope were used as continuous independent variables. The AUC for TWA, HRT onset, and HRT slope at 10 to 14 weeks after MI was 0.73. The AUC increased to 0.81 when LVEF at 8 weeks was added, indicating that LVEF provided information on prognosis additive to the noninvasive tests.

Optimal combination of parameters. Improved diagnostic accuracy, in terms of higher hazard ratio values (Table 5, right) and higher AUC values (Table 7) was observed when an LVEF <0.50 measured at 8 to 10 weeks after MI was combined with TWA plus HRT measured at 10 to 14 weeks after MI. Kaplan-Meier curves illustrating the utility of combining LVEF with TWA and either HRT or BRS are shown (Fig. 3).

Discussion

This is the first prospective study to assess the capacity of combined assessment of autonomic tone plus cardiac electrical substrate to predict the development of serious outcomes after MI. Impaired HRT plus abnormal TWA measured at 10 to 14 weeks after MI best identified patients at risk. This combination reliably predicted a higher risk of cardiac death or cardiac arrest, a higher risk of death from any cause, and a higher risk of fatal or nonfatal cardiac arrest.

Remodeling after MI and rationale for combined assessment. Similar to others (34,35), we observed a significant increase in LVEF over the initial 2 months after MI. This likely reflects the frequent use of early revascularization strategies and medications known to promote favorable LV remodeling (34). It is not surprising that the diagnostic value of the noninvasive parameters varied at 2 to 4 weeks versus 10 to 14 weeks after MI. To our knowledge, the diagnostic value of these parameters at serial points early after MI has not been reported previously.

Abnormalities of electrical substrate are thought to facilitate the initiation of serious arrhythmias, whereas modulating factors, such as autonomic tone, promote arrhythmia

Table 6 AUC, Test Characteristics, and Accuracy of the Noninvasive Parameters to Predict the Primary Outcome (Cardiac Death or Resuscitated Cardiac Arrest) at 10 to 14 Weeks Post-MI

Parameters (10 to 14 Weeks Post-MI)	Area Under the ROC Curve*	Characteristics (95% CI)		Predictive Accuracy (95% CI)	
		Sensitivity	Specificity	Positive	Negative
Abnormal exercise TWA + BRS (n = 52) vs. others	0.65	45 (39–49)	86 (82–90)	23 (18–28)	94 (92–96)
Abnormal Holter TWA + BRS (n = 53) vs. others	0.65	45 (39–49)	86 (82–90)	23 (18–27)	94 (92–97)
Abnormal exercise TWA + HRT (n = 91) vs. others	0.70	59 (53–64)	74 (70–79)	18 (14–23)	95 (92–97)
Abnormal Holter TWA + HRT (n = 93) vs. others	0.71	62 (57–67)	74 (70–79)	19 (15–24)	95 (93–98)

*Unadjusted logistic regression model for the pre-specified dichotomy limits (see Table 4).

Abbreviations as in Tables 4 and 5.

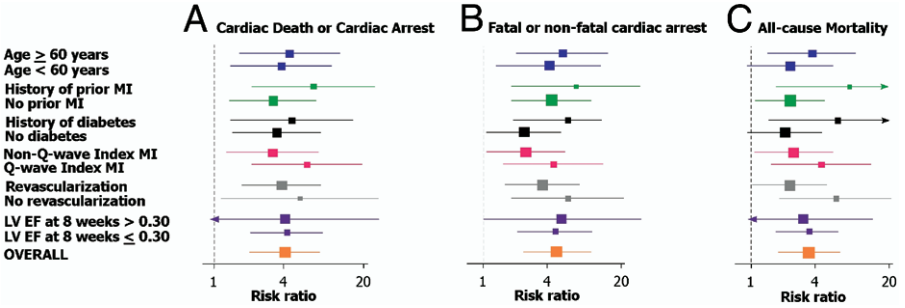

Figure 2 Predictive Value in Subgroups

The unadjusted risk of the primary outcome of cardiac death or resuscitated cardiac arrest **(A)** and the secondary outcomes of fatal or nonfatal cardiac arrest **(B)** and all-cause mortality **(C)** for patients with versus without both abnormal heart rate turbulence and abnormal Holter repolarization alternans are shown. The central estimate and 95% confidence interval for the hazard ratio in subgroups and overall are shown. LVEF = left ventricular ejection fraction; MI = myocardial infarction.

maintenance (36). Concomitant impairment of autonomic tone and electrical substrate would be anticipated to optimally identify patients at risk of serious arrhythmias. Our results show that post-MI patients with abnormal TWA plus either impaired BRS or HRT have a significantly higher risk of serious events compared with patients without both of these abnormalities. This finding was consistent within multiple patient subgroups.

Techniques evaluated in the REFINE study. Baroreflex sensitivity is a reliable measure of cardiac autonomic tone (9), and HRT is closely linked to BRS (37). Heart rate turbulence is often described in terms of the presence or absence of the normal acceleration in heart rate that follows a VPB (HRT onset) and the magnitude of the subsequent slowing in heart rate (HRT slope) (25). Repolarization alternans is a sensitive marker of underlying abnormalities in electrical structure. It is often assessed as a sustained, microvolt phenomenon with exercise (26). A negative exercise TWA result identifies patients at low risk of serious events, but a non-negative result is limited by poor positive predictive accuracy. Repolarization alternans can also be assessed as a transient phenomenon using ambulatory ECG recordings (13), but only sparse prospective data are available (38). We found similar predictive utility with exercise versus Holter assessment, but the overall level agreement between methods was modest. This indicates that the 2 methods may provide different prognostic information. The reasons for this may relate to when the tests were performed (during exercise vs. immediately after exercise), the size of the sampling window (128 beats with exercise TWA vs. 32 beats with Holter TWA), the level of ambient noise, or other factors.

Prior studies assessing the utility of combined parameter evaluation. Combined evaluation of HRV plus signal-averaged QRS in the initial month after MI was shown to enhance risk prediction in prior studies (15,18). However, these prior data were obtained in a different era of MI management and likely do not reflect contemporary practice. Similar to another study of contemporarily treated patients (19), combined assessment of autonomic tone plus signal-averaged ECG did not reliably predict outcome in the REFINE study.

The REFINE study versus other noninvasive risk stratification studies. Individual measures of severe autonomic impairment, when measured in the initial month after MI, have been shown to identify patients at risk of serious events. However, each is limited by low sensitivity. In the REFINE study the combination of impaired HRT plus

Table 7 AUC, Test Characteristics, and Accuracy of the Noninvasive Parameters Combined With LVEF to Predict the Primary Outcome (Cardiac Death or Resuscitated Cardiac Arrest) Beyond 8 Weeks Post-MI

Parameters (Beyond 8 Weeks Post-MI)	Dichotomized AUC*	Characteristics (95% CI)		Predictive Accuracy (95% CI)	
		Sensitivity	Specificity	Positive	Negative
Abnormal exercise TWA + BRS + LVEF <0.50 (n = 31) vs. others	0.71	37 (32–42)	93 (90–96)	32 (27–37)	94 (92–97)
Abnormal Holter TWA + BRS + LVEF <0.50 (n = 32) vs. others	0.71	37 (32–42)	93 (90–95)	31 (26–36)	94 (92–97)
Abnormal exercise TWA + HRT + LVEF <0.50 (n = 64) vs. others	0.72	52 (46–57)	83 (79–87)	23 (17–26)	95 (92–97)
Abnormal Holter TWA + HRT + LVEF <0.50 (n = 55) vs. others	0.74	55 (50–61)	86 (82–90)	27 (22–32)	96 (93–98)

*Unadjusted logistic regression model for the pre-specified dichotomy limits (see Table 4).
Abbreviations as in Tables 4 and 6.

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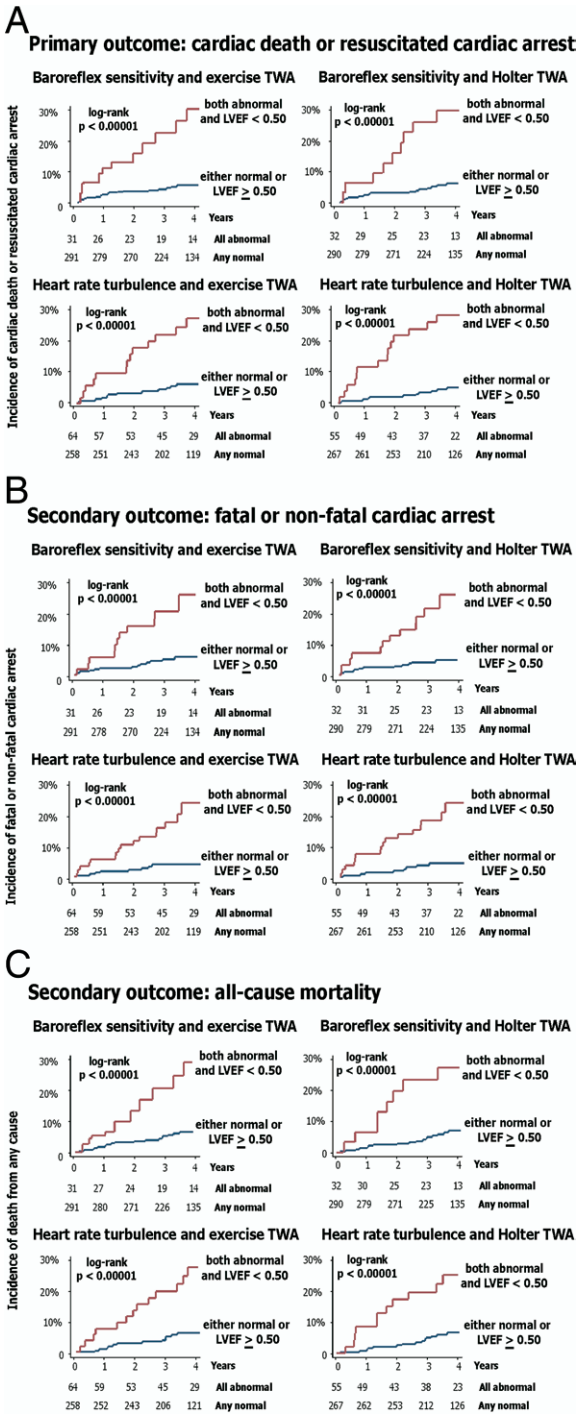

Figure 3 Risk Dichotomization

The risk of the primary outcome of cardiac death or resuscitated cardiac arrest **(A)** and secondary outcomes of fatal or nonfatal cardiac arrest **(B)** and all-cause mortality **(C)** among patients with impaired autonomic tone, measured using either baroreflex sensitivity or heart rate turbulence, plus abnormal repolarization alternans and an ejection fraction below 0.50 versus the remaining patients are shown. Numbers of patients in each group at the time points are indicated **below each graph**. TWA = T-wave alternans; other abbreviations as in Figure 2.

abnormal Holter TWA at 10 to 14 weeks after MI identified a similar risk of cardiac death to that of markedly abnormal BRS alone (9), but a larger proportion of patients at risk were identified (65% vs. 35%; exact p = 0.03). The method used in the REFINE study also identified a similarly high risk of cardiac death or cardiac arrest to severe HRT alone (14), but more patients at risk were identified using HRT plus TWA (62% vs. 32%; exact p = 0.03). The risk of death associated with HRT plus TWA is similar to that found for severe deceleration capacity alone (19), but more patients at risk are identified using HRT plus TWA versus deceleration capacity (57% vs. 30%; exact p = 0.006).

Noninvasive parameters and EF. An LVEF ≤0.30 measured at 8 to 10 weeks after MI predicted a 3-fold higher risk of the primary outcome, but only 31% of patients who developed the primary outcome had an LVEF ≤0.30. The combination of impaired HRT plus abnormal TWA predicted a >4-fold risk of the primary outcome and identified a significantly larger proportion of patients (exact p = 0.034). The predictive utility of TWA combined with either HRT or BRS was consistent among subgroups, including patients with LVEF values ≤0.30 versus >0.30 beyond the initial 8 weeks after MI (Fig. 2). Moreover, LVEF measured at 8 to 10 weeks after MI provided information on risk that was additive to that provided by HRT plus TWA. The 20% of patients with impaired HRT, abnormal exercise TWA, and an LVEF <0.50 beyond 8 weeks after MI had a 30% risk of cardiac death or cardiac arrest and a 27% risk of death over 4 years versus a 5% risk in the remaining 80% of patients. In contrast to other risk assessment approaches, the combination of HRT plus Holter TWA identified the majority of patients destined to suffer a cardiac arrest (67%) or die of any cause (57%).

Risk assessment in clinical practice. We found that a relatively simple testing protocol that included assessment of LVEF, a 24-h ambulatory ECG monitor, and a low-level exercise test beyond 8 weeks after MI readily identified the majority of patients destined to suffer serious events. Similar results were obtained with assessment of LVEF and a 24-h high resolution Holter. This simple, easy-to-implement screening strategy has significant clinical appeal. However, this approach, particularly Holter-based TWA assessment, requires validation.

Study limitations. This was a carefully conducted cohort study in a well-described group of contemporarily treated post-MI patients. Pre-specified rigorous methods were used, and the end points were independently adjudicated. However, this was not a randomized trial, and our results are subject to both known and unknown factors. Despite the apparent detection of patients at risk for serious arrhythmic events with the combination of TWA plus HRT in REFINE, a larger study found that HRT was not a specific marker for arrhythmic death (39). Exercise TWA has been shown to be predictive of death or serious arrhythmias (26), and may be a more specific marker for arrhythmic death (27). However, it is well known that categorizing deaths as

arrhythmic or nonarrhythmic is imperfect. Thus, overall mortality is considered by many to be a more appropriate outcome for assessing therapeutic efficacy (29). Nonetheless, the combination of abnormal TWA plus impaired autonomic tone reliably predicted the risk of the primary outcome of cardiovascular death or resuscitated cardiac arrest, as well as the secondary outcomes of all-cause mortality and fatal or nonfatal cardiac arrest in the REFINE study.

Conclusions

Patients with mild or greater LV dysfunction beyond the initial 8 weeks after MI who have both abnormal TWA and impaired autonomic tone are at greatly increased risk of serious events in follow-up.

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